

Applicant:	Ogari Pacheco et al	Conf.: 5587
Appl. No.:	10/517,453	Group: 1609
Filed:	December 9, 2004	Examiner: Huang, G. G.
For:	SOLUBLE, STABLE, AND CONCENTRATED PHARMACEUTICAL COMPOSITIONS COMPRISING RITONAVIR AND PROCESS FOR PREPARING THEREOF (as amended)	

DECLARATION UNDER 37 CFR 1.132

Ogari de Castro PACHECO declares that:

[001]. I am a founding partner of CRISTÁLIA PRODUTOS QUÍMICOS FARMACÊUTICOS LTDA, the assignee of the entire rights title and interest in the above-identified patent application and the invention described therein.

[002]. I received a doctor degree in 1964 from the School of Medicine of the San Paulo University (in Portuguese, Universidade de São Paulo), from San Paulo, Brazil. In 1966, I received a postgraduate degree in surgery of the digestive tract from the Hospital of Clinics of the School of Medicine of the San Paulo University.

[003]. I have full knowledge of the disclosure of the above-identified patent application and the field of art of the present invention. I have read and understand the January 27th, 2009 Office Action and the references cited therein.

This Declaration:

- ✓ Provides experimental data comparing the composition of the present invention with the composition from the cited references US 6,232,333, (hereinafter Lipari) and US 6,008,228, (hereinafter Bailey)
- ✓ Demonstrates the effect of the different ingredients and their respective amounts from each reference.
- ✓ Demonstrates the significance of the claimed process for preparing the composition of the present invention.
- ✓ Demonstrates that the loss of ritanovir in the claimed process during the filtration step is insignificant.
- ✓ Illustrates pictorially the solutions before and after the filtration step of the claimed process.
- ✓ Provides my conclusion, supported by the experimental data presented herein, that one of skill in the art could not arrive at the present invention based on the combined disclosures of Lipari and Bailey.

A. The Compositions of the Prior Art

[004]. The main points, taking in account each cited reference, are that Bailey provides the usage of C₈-C₁₀ medium chain mono/diglycerides mixture as the solvent in the composition of a HIV protease inhibitor as does the present invention composition, and Lipari teaches the usage of long chain (C₁₂-C₁₈) fatty acid alone or in combination with an alcohol as solvent in a composition of ritonavir.

[005]. The compositions of the three references can be summarized as follows:

Applicant's Invention (as amended)	Lipari	Bailey
Ritonavir <u>Amount</u> : 10% to 30%.	Ritonavir <u>Amount</u> : 1% to 50%.	Saquinavir, "compound A" ¹ <u>Amount</u> : 50mg to 400 mg (preferably 200 mg – that represents 20% of saquinavir in the examples' compositions).
Mixture of alcoholic solvent and alcoholic co-solvent (preferably ethanol and propylene glycol). <u>Amount</u> : 22% (total mixture). 12% (ethanol) 10% propylene glycol	An alcohol is optionally added to the long chain fatty acid (preferably ethanol or propylene glycol). <u>Amount</u> : up to 15% (when there is mixture of ethanol and propylene glycol the amount of the total mixture is 10% (5% each) (column 11, lines 49-51 and example 35).	
C ₈ -C ₁₀ chain mono/diglycerides. <u>Amount</u> : 20% to 40%.		At least one monoglyceride of medium chain, also can be mixture of mono/ di/ triglyceride (preferably of C ₈ -C ₁₀ . <u>Amount</u> : 40% to 80%.
Surfactant (preferably polyethoxylated castor oil 35). <u>Amount</u> : 5% to 10%.	Surfactant (preferably polyoxyl 35 castor oil and Tweens). <u>Amount</u> : 0% to 40%.	
Antioxidant (preferably butylated hydroxy toluene or alpha-tocopherol). <u>Amount</u> : 0.01% to 0.1%.	Antioxidant (preferably butylated hydroxy toluene). <u>Amount</u> : 0.01% to 0.08%.	Antioxidant (preferably alpha-tocopherol) <u>Amount</u> : 0.01% to 0.5%.

¹ N- tert- butyl- decahydro- 2- [2 (R)- hydroxy- 4- phenyl- 3- (S)- [[N- (2- quinolylcarbonyl)- L- asparginy] amino] butyl]- (4aS, 8aS)- isoquinoline- 3- carboxamide. (Saquinavir)

B. Bailey v. Present Invention

[006]. For proper comparison tests, the composition of Bailey was reproduced replacing saquinavir by ritonavir.

[007]. The specific formulations investigated by the present tests were elected according to the proximity of ingredients and their correspondent amounts as described in each document and also taking in account the amendments limiting the instant invention scope. The formulations investigated are described at table 1.

Table 1 – Bailey composition vs instant invention representative composition (referring to experiments 1 and 2 of the present Declaration)

Ingredient	Quantity in grams	
	Formulation A25 from the US 6,008,228 (A25)	Formulation of Example 5 from the instant application (Ex5)
Ritonavir	40*	40
Medium chain mono/diglyceride (Akoline®)	80	46.975
Antioxidant	1 (alpha-tocopherol)	0.05 (BHT)
Polyvinylpyrrolidone K30 (PVP K30)	4	-
Ethanol	-	24 [#]
Propylene glycol	-	20
Castor oil polyethoxylated (Cremofor®)	20	20
PEG400	55	46.975
Water	-	2
Total	200	200

* ritonavir was used in place of saquinavir.

[#] Final amount of ethanol in the formulation. Before evaporation step, it has been used 48g of ethanol for dissolving ritonavir when the formulation was prepared by the instant invention process.

Experiment 1: The Composition of Bailey using ritonavir prepared by the Method of Bailey:

[008]. Preparation of composition A25 from Bailey (see column 27, lines 10-17 of US 6,008,228) was carried out by:

- mixing the medium chain mono/diglycerides mixture, PEG 400, castor oil 40 polyethoxylated and polyvinylpyrrolidone K30 in a suitable vessel with stirring and heating to approximately 50°C (Figures 1A and 1B);
- adding the active ingredient (for the present test ritonavir was used in the place of saquinavir) and maintaining the stirring in order to verify if total dissolution of ritonavir is possible.

Results: When using the direct addition method of Bailey, the composition of Bailey (A25) did not dissolve, even after constant stirring and maintenance of temperature at ~60°C, for 12 hours (**Figure 1C**). After the composition of Bailey returned to room temperature, the solution did not become clear (**Figure 1D**). The dl-alpha-tocopherol was not added to the container since the mixture (**Figure 1C and 1D**) did not become a clear solution.

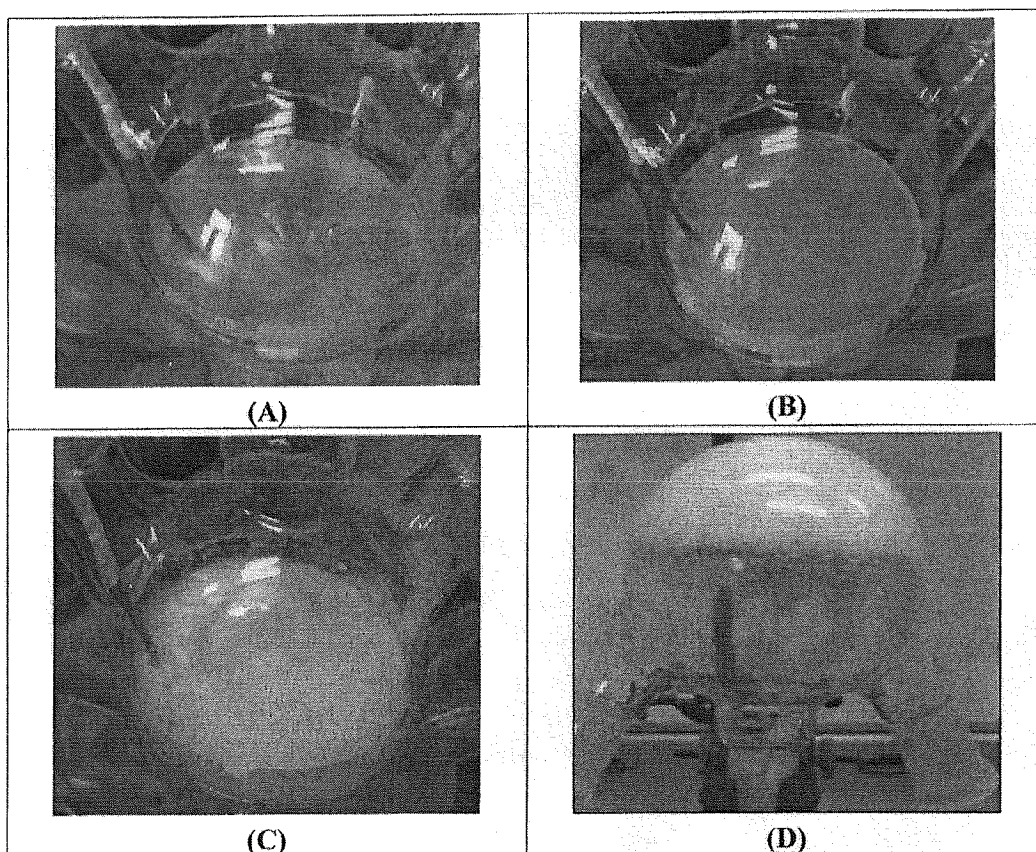


Figure 1. Formulation A25 from Bailey comprising ritonavir in place of saquinavir. (A) clear solution obtained by mixing C₈-C₁₀ medium chain mono/diglycerides mixture, PEG 400 and castor oil polyethoxylated; (B) mixture obtained after addition of polyvinylpyrrolidone K30 to the solution shown in panel (A) but a clear solution was obtained after stirring for 45 min at 50°C (C) mixture obtained after addition of ritonavir to the solution demonstrating that ritonavir does not dissolve in the medium even after 12 hours of constant stirring and temperature maintained at ~60°C; (D) solidified formulation obtained after the mixture shown in (C) attained the ambient temperature.

Experiment 2: Comparison of the Composition of the present invention using two different processes.

[009]. The formulation of the Example 5 (Ex5) from the present application was prepared by two different ways, in order to demonstrate the relevance of the procedure steps sequence to the final composition of ritonavir.

(i) Composition of the present invention obtained by the method of the instant invention.

[0010]. The formulation of the Example 5 (Ex5) from the present application was prepared as following:

- ritonavir was totally dissolved in 48 grams of ethanol at 30-45°C (Figure 2A), followed by the filtration of the resulting solution (to remove non visible solid particles from the medium);
- the solution of ethanol and ritonavir was concentrated by rotoevaporation, wherein ethanol excess was removed under reduced pressure at a temperature of about 40°C until its amount achieves the desired ethanol content in the final composition (Figure 2B);
- the ingredients propylene glycol, C₈-C₁₀ medium chain mono/diglycerides mixture, BHT, PEG 400 and water were added to the system that remained under stirring until the mixture became a clear solution (Figure 2C);
- castor oil 35 polyethoxylated was then added;
- the system was stirred until the mixture became a clear solution (if necessary, ethanol is used for correcting the final composition weight).

Results: The resulting formulation of the present invention is illustrated in Figure 2D wherein it is possible to note that it is totally clear and soluble.

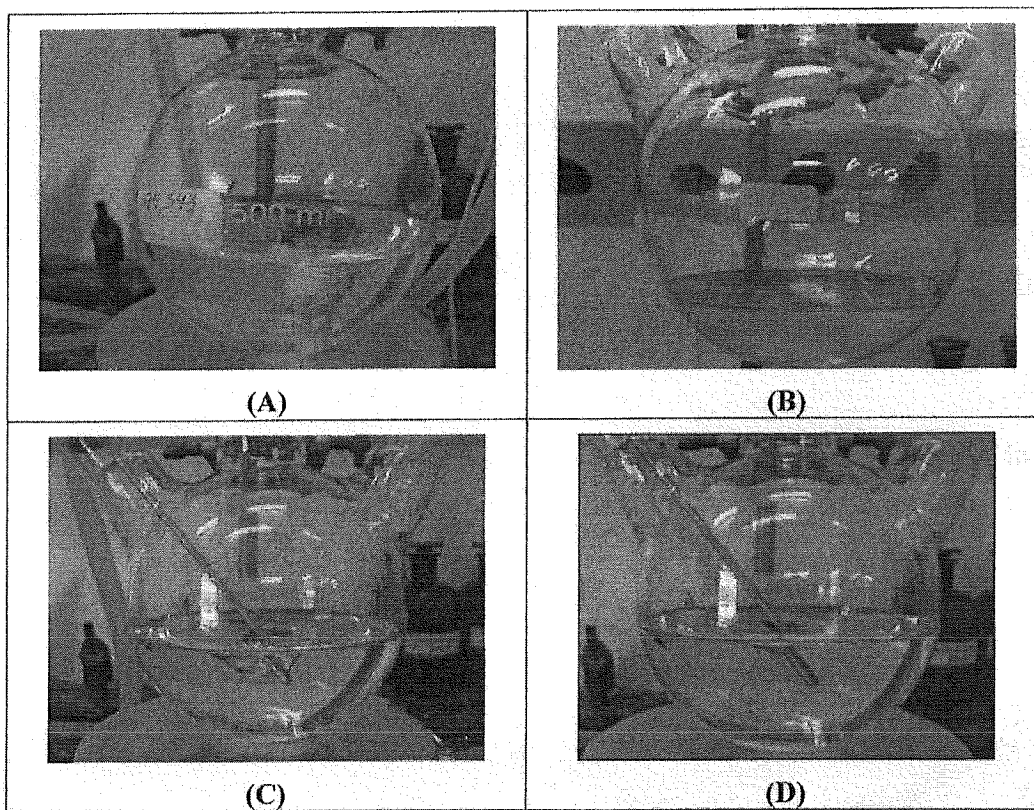


Figure 2. Formulation Ex5 of the instant invention. (A) clear solution obtained by dissolution of ritonavir in ethanol; (B) clear solution obtained after filtration and concentration by rotoevaporation of the solution shown in panel (A); (C) clear solution obtained after addition of excipients (propylene glycol, C₈-C₁₀ medium chain mono/diglycerides mixture, BHT, PEG 400 and water) to the solution shown in panel (B); (D) clear solution obtained after addition of Castor oil 35 polyethoxylated (final composition).

(ii) *Composition of the present invention obtained by a method different from the instant invention method.*

[0011]. The formulation Ex5 of the present application was also prepared by

- adding propylene glycol, ethanol, C₈-C₁₀ medium chain mono/diglycerides mixture, BHT, PEG 400 and water to the system;
- stirring until the mixture became a clear solution (**Figure 3A**);
- adding ritonavir to the container;
- stirring the mixture under heat at a temperature of 30-45 °C for 16 hours (**Figure 3B**);

- adding castor oil 35 polyethoxylated and mixing (Figure 3C).

Note that this method does not include the pre-dissolution of ritonavir in ethanol nor the subsequent filtration and rotoevaporation steps that are exclusive features of the instant application process.

[0012].Results: The ingredients propylene glycol, ethanol, C₈-C₁₀ medium chain mono/diglycerides mixture, BHT, PEG 400 and water were added to the system that remained under stirring until the mixture became a clear solution (Figure 3A). Ritonavir was added to the container and the mixture was stirred in order to verify if total dissolution of ritonavir is possible. It was observed the non-dissolution of ritonavir in the medium, even after stirring for 16 hours at ~42°C (Figure 3B). Even so, the castor oil 35 polyethoxylated was then added to the container and mixed in order to verify if the mixture became a clear solution. The resulting formulation is illustrated in Figure 3C wherein it is possible to note that, by this process, the formulation of Example 5 (Ex5) is not clear and soluble as desired, demonstrating that the pre-dissolution of ritonavir in ethanol and the subsequent filtration and rotoevaporation steps of the instant invention process are *essential* to provide the final formulation of the Example 5 (Ex5) as a clear solution.

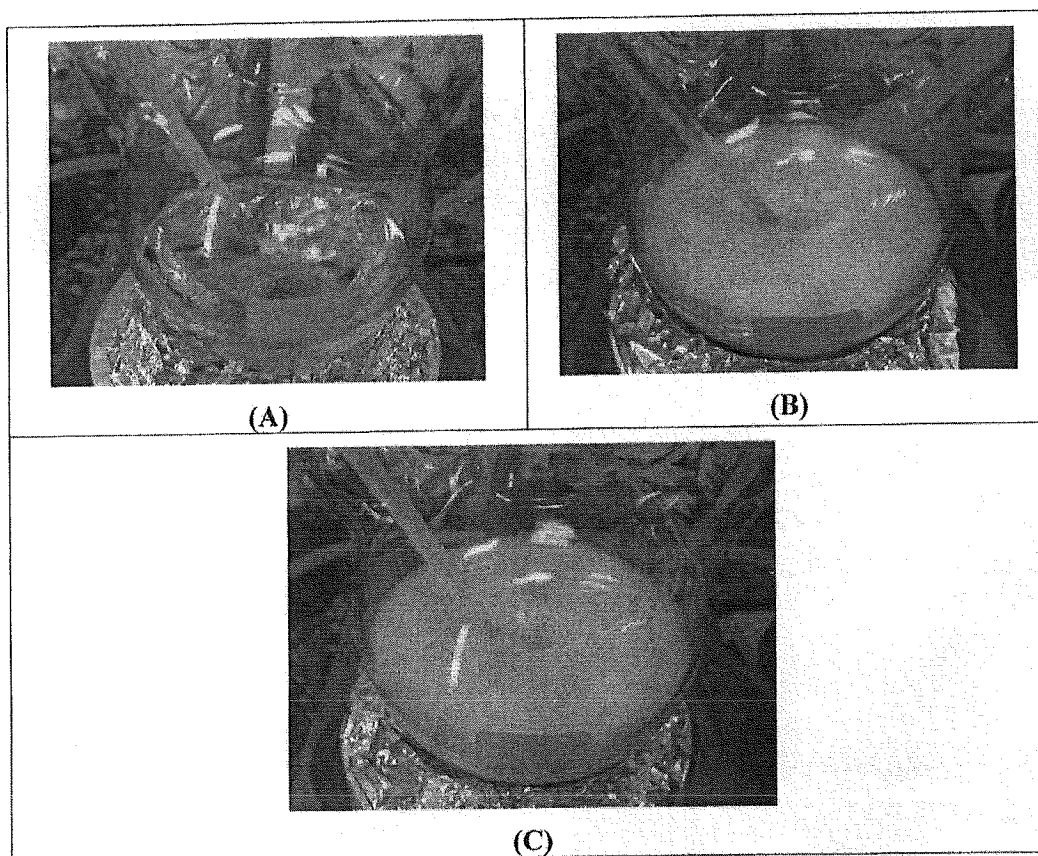


Figure 3. Formulation Ex5 of the instant invention. (A) clear solution obtained by mixing propylene glycol, C₈-C₁₀ medium chain mono/diglycerides mixture, BHT, PEG 400 and water; (B) mixture obtained after addition of ethanol and ritonavir to the solution shown in panel (A) demonstrating that ritonavir does not dissolve in the medium even after 16 hours of stirring and temperature maintained at ~42°C; (C) mixture obtained after addition of castor oil 35 polyethoxylated to the mixture shown in panel (B) demonstrating that the final composition can not be obtained as clear solution if the preparation process is different from the instant invention process.

C. Lipari v. the present invention.

Experiment 3: Comparison of a Modified composition of the present invention using two methods of preparation.

[0013]. To compare the composition of Lipari to the presently claimed composition, we have substituted the medium chain mono/diglycerides mixture of the present invention for the long chain fatty acids found in the disclosure of Lipari. (See Table 2). This substitution parallels the Examiner's analysis of the combination of Lipari and Bailey, because the Examiner suggests that one of skill would find it obvious to substitute the fatty acid of Lipari with the mono/diglycerides mixture of Bailey. Accordingly, we believe that the solution we tested is even closer to the claimed invention than the composition of Lipari.

[0014]. The modified formulation of the Example 5 (Ex5) from the present application, wherein oleic acid was used in place of C₈-C₁₀ medium chain mono/diglycerides mixture. The ingredients were combined two different ways in order to demonstrate the relevance of the procedure steps sequence to the final composition of ritonavir.

Table 2 – Instant invention representative composition vs instant invention composition replacing Akoline[®] by oleic acid (Lipari) (referring to experiment 3 (i)-(iii))

Ingredient	Quantity in grams	
	Formulation of Example 5 from the instant application (Ex5)	Formulation of Example 5 from the instant application (Ex5) replacing Akoline [®] by oleic acid
Ritonavir	40	20
Medium chain mono/diglyceride (Akoline [®])	46.975	-----
Oleic acid	-----	23.488
Antioxidant	0.05 (BHT)	0.025
Ethanol	24 [#]	12 [#]
Propylene glycol	20	10
Castor oil 35 polyethoxylated (Cremofor [®])	20	10
PEG400	46.975	23.488
Water	2	1
Total	200	100

[#] Final amount of ethanol in the formulation. When the formulation was prepared by the instant inventive process, before evaporation step, 24 grams of ethanol was used for dissolving ritonavir. Note that the method of Lipari does not disclose pre-dissolving the ritonavir in alcohol.

(i) *Modified composition of the present invention obtained by the method of the instant invention.*

[0015]. The formulation of the Example 5 (Ex5) from the present application was prepared by the process of the present application with the difference that oleic acid as in Lipari was used in place of C₈-C₁₀ medium chain mono/diglycerides mixture used in the present invention. The composition was prepared as follows:

- ritonavir was dissolved in 24 g ethanol at 30-45°C (Figure 4A),
- the ethanol/ritonavir solution was filtered in order to remove non-visible solid particles from the medium (Figure 4B),
- the ritonavir/ethanol solution was concentrated in order to remove the ethanol excess (this step is completed when the amount of ethanol achieves the desired ethanol content in the final composition).
- propylene glycol, oleic acid, BHT, PEG 400 and water were added to the concentrated ethanol/ritonavir solution while stirring
- the composition was stirred until the mixture became a clear solution.
- castor oil 35 polyethoxylated was added while stirring
- the composition was stirred until the mixture became a clear solution (Figure 4C) (if necessary, ethanol is used for correcting the final composition weight).

Results: The resulting formulation is illustrated in Figure 4D wherein it is possible to note that it is clear and soluble.

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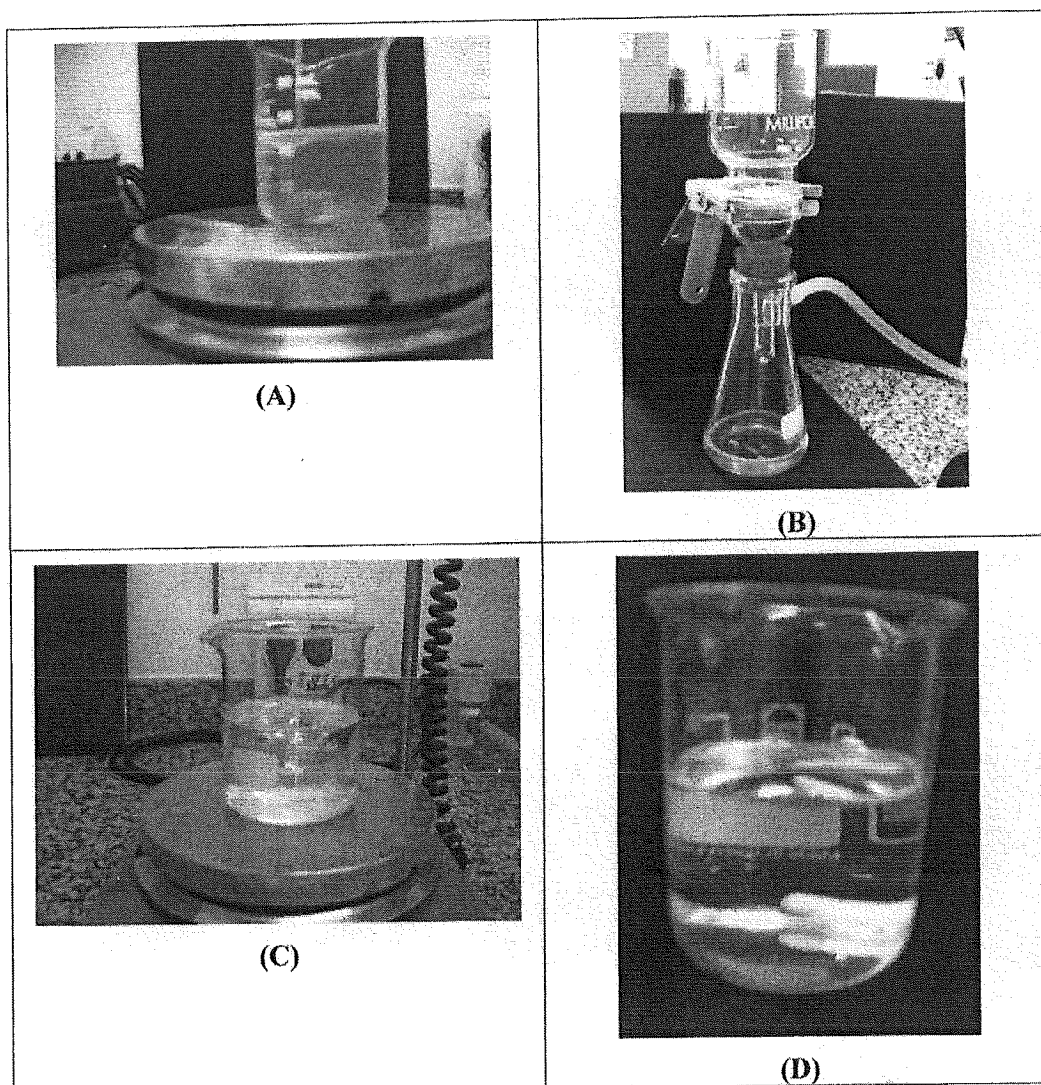


Figure 4. Modified formulation **Ex5** of the instant invention. **(A)** clear solution obtained by dissolution of ritonavir in ethanol; **(B)** clear solution obtained after filtration of the solution shown in panel (A), the filtrate is concentrated for removing the excess of ethanol added in the first step; **(C)** clear solution obtained after addition of excipients (propylene glycol, **oleic acid**, BHT, PEG 400, castor oil 35 polyethoxylated and water) to the filtrate shown in panel (B); **(D)** clear solution (final composition).

(ii) The modified composition prepared by the inventive method is not stable

[0016]. The composition containing oleic acid (discussed in Experiment 3(i) above) was then fractioned into vials and stored for 48 hours either at room temperature or in a refrigerator.

[0017]. Results: The modified formulation (**Ex5**) is not stable enough since it showed flocculation after 48h of storage at ambient temperature (**Figure 5**, flask on

the left side); in the same period, the same formulation stored in the refrigerator stays clear (**Figure 5**, flask on the right side). In the same condition of storage, the original formulation of example 5 of the presently claimed invention prepared by the process of the instant invention is stable for at least 6 months (please see table on page 37 of the specification as filed).

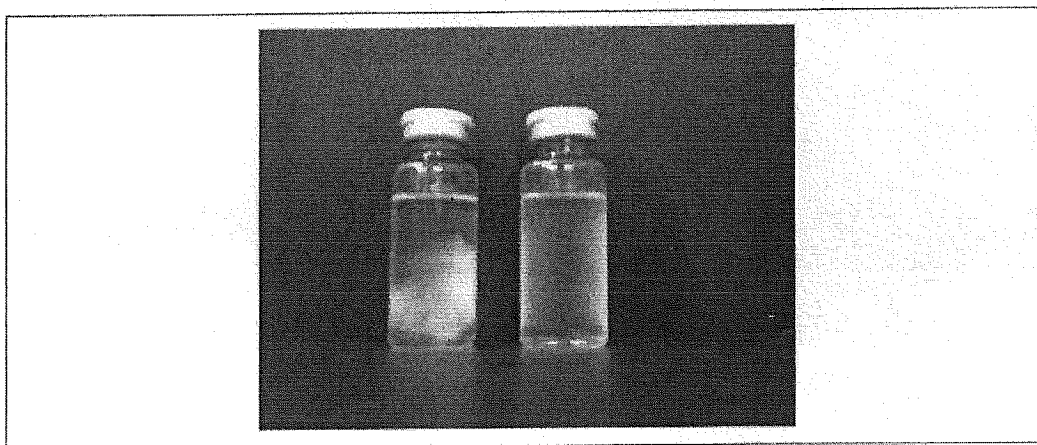


Figure 5. Modified formulation Ex5 of the instant invention wherein oleic acid was used in place of C₈-C₁₀ medium chain mono/diglycerides mixture. Flask on the left side: final composition stored for 48h at room temperature (25°C ± 2°C). Flask on the right side: final composition stored for 48h under refrigeration (5°C ± 3°C).

(iii) Modified composition of the present invention obtained by the method of Lipari.

[0018]. The process of Lipari is described, for example, at column 23 lines 21-34 of US 6,232,333. We adapted the process to account for the formulation of the modified composition of the present invention (i.e., it includes oleic acid rather than a C₈-C₁₀ medium chain mono/diglycerides mixture). The process was conducted as follows:

- oleic acid, ethanol, propylene glycol, and PEG 400 were mixed in a container **(Figure 6A)**;
- the mixture was warmed to about 33°C (28-37°C) and maintained at that temperature;
- BHT was added to the container maintaining the mixture under stirring until the mixture became a clear solution;
- ritonavir was slowly added to the container and the mixture was mixed for 9 hours at ~37°C **(Figure 6B)**;
- castor oil 35 polyethoxylated and water were then added to the container and mixed;
- the mixture was allowed to cool to 10-30°C **(Figure 6C)**.

Results: Mixing the excipients only, i.e., oleic acid, ethanol, propylene glycol, PEG 400 and BHT and heating to about 33°C (28-37°C) resulted in a clear mixture. **(Figure 6A)**. Once ritonavir was added it was observed that ritonavir did not dissolve in the medium, even after stirring for 9 hours at ~37°C **(Figure 6B)**. To ensure that the castor oil 35 polyethoxylated and water did not affect the solubility of ritonavir those components were also added with heat. However, even once heating was discontinued and the final composition allowed to cool to 10-30°C the ritonavir had not dissolved. **(Figure 6C)**. Accordingly, using the method of Lipari with a composition similar to the instant invention but including oleic acid did not result in the product of the present invention. Furthermore, it resulted in a product which would not be used by one of skill in the art.

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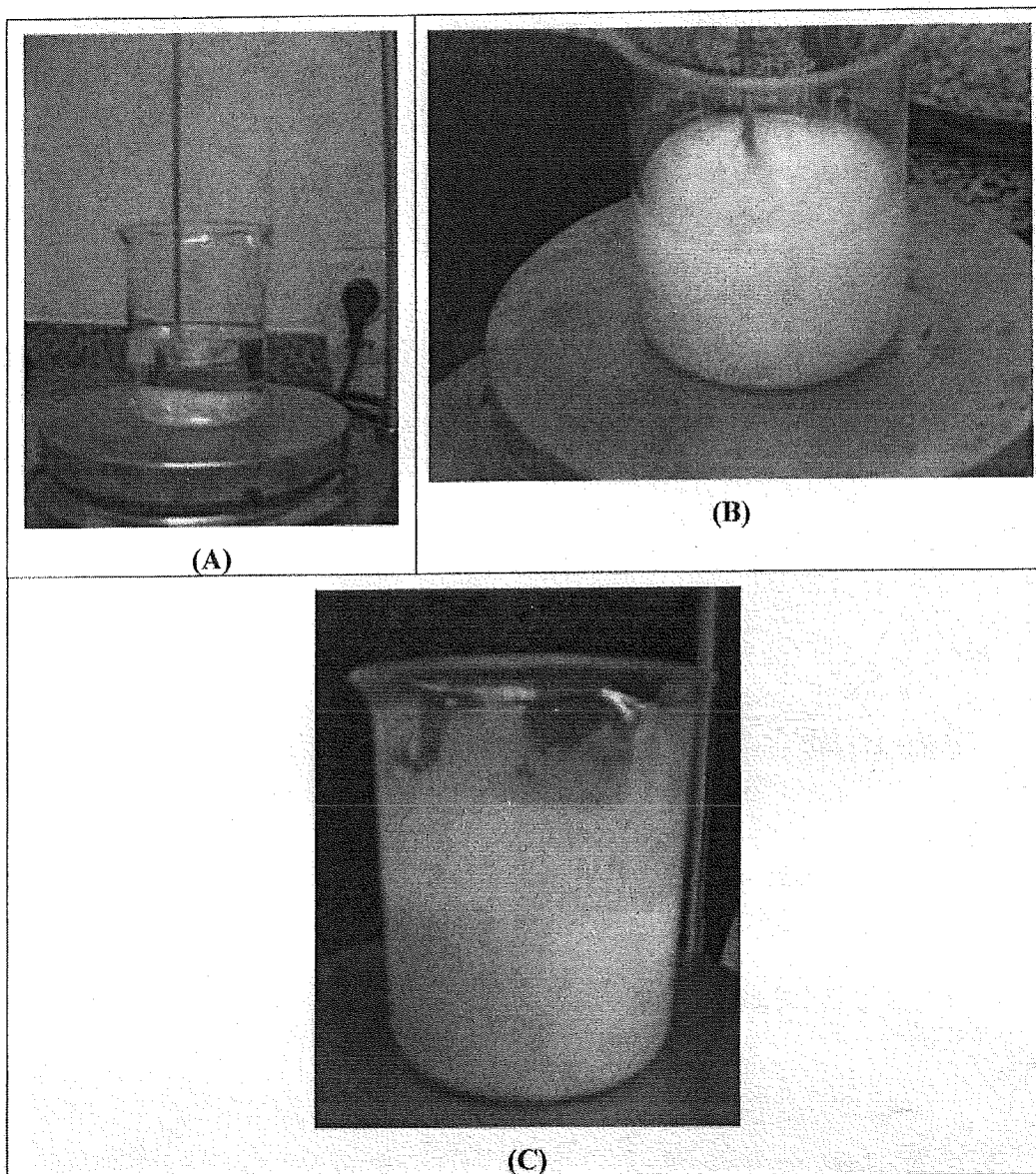


Figure 6. Modified formulation Ex5 of the instant invention. (A) clear solution obtained by mixing ethanol, propylene glycol, oleic acid (in place of C_8 - C_{10} medium chain mono/diglycerides mixture), and PEG 400; BHT was added and mixed until the solution was clear; (B) mixture obtained after slow addition of ritonavir to the solution shown in panel (A) demonstrating that ritonavir does not dissolve in the medium even after 9 hours of stirring and temperature maintained at $\sim 37^\circ\text{C}$; (C) mixture obtained after addition of castor oil 35 polyethoxylated and water to the mixture shown in panel (B) demonstrating that the final composition can not be obtained as clear solution if the preparation process is different from the instant invention process.

D. The Filtration Step

Experiment 4: The filtration step of the present invention does not significantly affect the final concentration of ritonavir

[0019]. The Examiner has indicated that because the present claims recite a final concentration, the claims are indefinite. The Examiner has suggested adding a starting amount of ritonavir to the claims. We present this experiment to show that the final amount of ritonavir does not significantly differ from the beginning amount of ritonavir. Thus, one of skill would find that the presently claimed inventive process and product is definite as described in the claims.

[0020]. In accordance with the instant application, the filtration of the ritonavir ethanolic solution aims to guarantee the absence of solid particles that can trigger the precipitation process later (Specification, page 17 lines 28-31). In the present case, the composition in the form of a solution is intended for oral administration. Therefore, filter paper can be used.

[0021]. A solution comprising 20g of ritonavir and 24 g of ethanol was filtered through a filter paper (*Quantitative, white, Ref. 40, F. Maia, able to retain particles higher than 8 μ m*), and the amount of particles retained by the filter was of 0.0625g (Figure 7). Assuming that all of the retained particles are ritonavir, we estimate a loss of about 0.3% of ritonavir which can be considered insignificant to the content of ritonavir in the final composition.

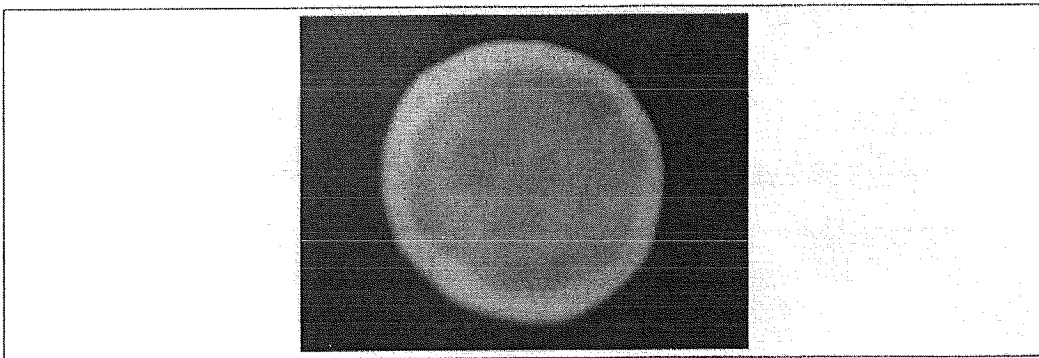


Figure 7. Filter view after the filtration of ritonavir ethanolic solution in accordance with the process of the instant invention.

[0022]. In the claimed method, one of skill in the art would recognize how much ritonavir was added initially, and also know to establish how much ritonavir is in the final composition. As ritonavir is not added in any other step in the presently

claimed method and can only possibly be removed by the filtration step, one of skill would find the presently claimed method clearly described by the claims. Accordingly, it is my opinion that the claims which recite a final concentration, weight/weight of ritonavir would be clear to one of skill in the art.

E. Conclusions

Conclusion: The US patent 6,008,228 (Bailey) cannot be used to establish a *prima facie* case of obviousness.

[0023]. The above-mentioned comparison tests clearly demonstrate that the Bailey reference does not teach either ritonavir compositions or the process for obtaining clear and soluble ritonavir compositions.

[0024]. The attempt to extrapolate Bailey's compositions to be employed with ritonavir instead of saquinavir showed that this strategy is absolutely not possible, once the resulting composition did not turn into a clear and soluble solution (**Figure 1**). The pictures in the Figure 1 agree with the statements about that reference on page 8 lines 12-15 of the specification as filed.

[0025]. The tests evidence that one having skill in the art cannot be able to produce clear and soluble compositions of ritonavir using Bailey's teachings. Therefore, the Bailey reference cannot be used to establish a *prima facie* case of obviousness in the present case.

Conclusion: The instant invention composition and process for preparing thereof is not an obvious substitution of one ingredient for another from the composition of US 6,232,333 (Lipari)

[0026]. The comparative results between the process of Lipari and the process of the instant invention for preparation of a modified Ex.5 composition comprising oleic acid in the place of Akoline® (**Figure 8**) demonstrate that the instant invention composition is not a mere or obvious substitution of a long chain (C₁₂-C₁₈) fatty acid of Lipari by a C₈-C₁₀ medium chain mono/diglycerides mixture since, even with such substitution, the process of the instant invention is essential in order to obtain a clear

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and soluble composition. Even if the process of the invention is used with Lipari's ingredients, the resulting composition is not stable, unlike the composition of the present invention. Therefore, Lipari's reference cannot be used to establish a *prima facie* case of obviousness in the present case.

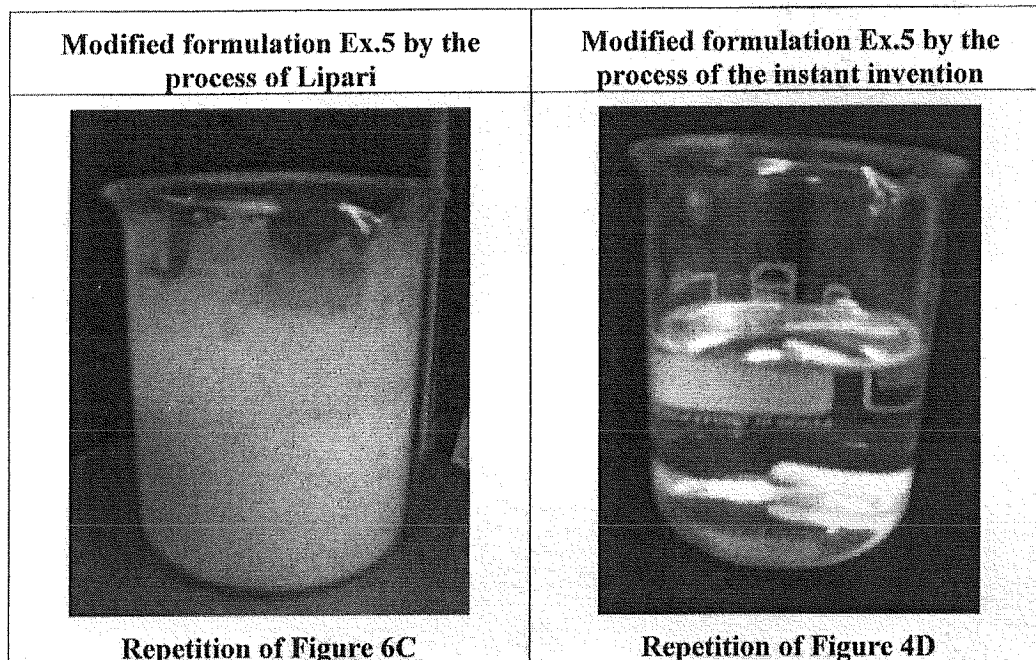


Figure 8. Modified formulation Ex5 of the instant invention obtained by the process of Lipari (repetition of Figure 6C) and by the process of the instant invention (repetition of Figure 4D).

[0027]. The original **Ex5** formulation according to the present application is obtained only if all the steps of the instant invention process are followed, in order, specifically including the steps of pre-dissolution of ritonavir in excess volume of ethanol, filtration and rotoevaporation for concentrating the ritonavir ethanolic solution. Furthermore, the ingredients of the instant invention must also be used to obtain a stable composition. (Please compare Figure 2D vs 3C).

Conclusion: The combination of the Method of Lipari with vacuum evaporation of CU Boulder does not make the present invention obvious.

[0028]. While the Examiner cites CU Boulder for the concept of vacuum evaporation, based on the methods of Lipari, ritonavir is never dissolved in ethanol alone. (Lipari, column 23, lines 21-35). Thus, vacuum evaporation would be performed on the entire composition. In our opinion the addition of rotoevaporation

from CU Boulder to the method of Lipari does not make the present invention obvious because the method of Lipari does not disclose the pre-dissolution of ritonavir in ethanol.

Conclusion: There are no teachings for one skilled in the art to combine both references cited by the Examiner (US patent 6,232,333 and US patent 6,008,228)

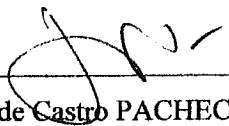
[0029]. One might consider that a person of skill in the art who reads Bailey and Lipari would expect that a C₈-C₁₀ medium chain mono-diglyceride (Bailey) could replace long chain (C₁₂-C₁₈) fatty acid (Lipari) in a composition of ritonavir and could eliminate an alcoholic co-solvent (Lipari). But, the present Declaration shows that the teachings of Bailey do not work for a composition of ritonavir. After this observation, one of skill in the art would expect that the composition of ritonavir needs an alcoholic solvent or co-solvent besides the medium chain mono-diglyceride. The present Declaration shows that said combination of ingredients is not sufficient to provide a concentrated and soluble pharmaceutical composition of ritonavir, being the composition with this characteristics obtained only by the process of the instant invention. So there is evidence that the instant invention is not reachable by a combination of the cited prior art references.

[0030]. The results that the process steps as presently claimed are necessary to obtain a clear solution of ritonavir, and that use of the C₈-C₁₀ medium chain mono-/diglycerides mixture is necessary to obtain a stable composition are unexpected by one of ordinary skill in the art of drug formulation who reads the Bailey and Lipari references.

[0031]. Considering the results and arguments above, I believe that the one of skill could not obtain the present invention either from the separate disclosures of Bailey and Lipari or from their combination. Accordingly, we believe that the present invention would not be obvious to one of skill in the art based on the combined disclosure of Bailey and Lipari.

[0032]. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed by me in Itapira-São Paulo, Brazil, this 25th day of June, 2009



Ogari de Castro PACHECO